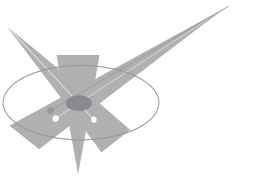
Rep Pract Oncol Radiother, 2006; 11(4): 169-174



Original Paper

Received: 2004.11.16
Accepted: 2006.05.26
Published: 2006.08.31

Classical prognostic factors in patients with non-advanced endometrial cancer treated with postoperative radiotherapy

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Aim Analysis of classical prognostic factors in patients with non-advanced endometrial cancer treated with postoperative radiotherapy.

Materials/Methods In the years 1985–1999, 705 patients underwent postoperative radiotherapy due to endometrial cancer: 529 patients with FIGO stage I and 176 with FIGO stage II cancer. Mean age was 58 years. In 96% of patients endometrioid adenocarcinoma was found. In 49.9% the cancer had a high, in 27.9% a medium, and in 22.2% a low degree of differentiation.

Results 82% of patients had 5-year disease-free survival. In univariate analysis a significantly higher rate of disease-free survival was observed in: patients younger than 60, with moderately and well differentiated cancers, with stage I endometrioid adenocarcinoma with less than 50% myometrial invasion. In multivariate analysis degree of cancer differentiation was the only independent prognostic factor.

Conclusions In a group of patients with non-advanced endometrial cancer treated with postoperative radiotherapy, degree of cancer differentiation is the primary prognostic factor.

Key words **non-advanced endometrial cancer • postoperative radiotherapy • prognostic factors**

Full-text PDF: http:/www.rpor.pl/pdf.php?MAN=9518
Word count: 1786
Tables: 2
Figures: –
References: 40

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Background

Surgical treatment is the procedure of choice in women with non-advanced endometrial cancer [1–4]. Indications for postoperative radiotherapy are assessed based on a set of prognostic factors which allow the patient to be qualified to one of three groups according to the level of risk of recurrence: low-risk, intermediate-risk, or high-risk [2–4].

Numerous prognostic factors are presented in the literature for this group of patients, including: age, state of their hormone receptors, stage of the cancer according to FIGO, cancer differentiation degree, depth of myometrial invasion, vascular invasion, cervical involvement, cancer type based on cellular classification [1,4–0]. However, all the authors consistently list only a few of the factors, based on multivariate analysis, as having independent prognostic value. The detailed levels of prognostic value of these factors are still being discussed (e.g. age, degree of differentiation, depth of myometrial invasion).

Sporadically, other prognostic factors are also found in the literature, such as weight, ethnicity, obstetric history, duration of clinical symptoms, and size of the primary tumour [1,4,5,11,12].

A separate group of potential prognostic factors, currently widely presented and discussed, includes markers studied using immunohistochemical, cytofluorometric and molecular biology techniques, e.g. DNA ploidy, proliferation index, S-phase fraction, MIB-1 (Ki-67), expression of p53 and HER 2/neu genes, angiogenesis, etc. [1,8,13–17].

Aim

The aim of the present study was the analysis of classical prognostic factors in patients with non-advanced endometrial cancer treated with postoperative radiotherapy.

Materials and Methods

There were 895 patients with endometrial cancer treated in the Centre of Oncology in Kraków between 1985 and 1999. 752 (84.0%) were diagnosed with non-advanced stage I or II cancer according to FIGO 1988 staging (18). 47 (5.2%) were diagnosed with well or moderately differentiated stage IA cancer; this group was treated with surgery alone. The remaining 705 (78.8%) patients with endometrial stage IA (poorly differentiated), IB, IC and II were treated with combination therapy: surgery followed by postoperative irradiation; and for this group a detailed analysis of classical prognostic factors was performed.

The youngest patient in the study group was 30, and the oldest was 80 years old; mean age was 58 years, median 59 years. Duration of presence of symptoms ranged from 1 to 108 months; mean 8 months, median 4 months. In our group 17.9% of women were nulliparous, 15.9% were uniparous, 29.1% biparous and 37.1% had a history of 3 or more births. In 676 (95.9%) women endometrioid adenocarcinoma was found, in 10 (1.4%) clear cell cancer, in 8 (1.1%) serous cancer, in 4 (0.6%) mucinous and in 7 (1.0%) other cancer types. 59% of patients had a haemoglobin level below 13g/dl, and the remaining 41% had a level of 13g/dl or higher.

In 75% of patients endometrial stage I cancer was found, and among this group: in 21 (3.0%) IA, in 180 (25.5%) IB and in 328 (46.5%) IC. In 25% of the studied women endometrial stage II cancer was found, and among this group: in 85 (12.1%) IIA, and in 91 (12.9%) IIB. In almost half of cases (49.9%) the cancer was well, in 27.9% moderately and in 22.2% poorly differentiated. In 21 (3.0%) patients invasion of the cancer was limited to the endometrium; in 297 (42.1%) myometrial invasion was below and in 387 (54.9%) was above 50% of myometrial thickness.

All patients underwent a classical, total, abdominal hysterectomy with bilateral salpingo-oophorectomy and postoperative radiotherapy. During surgery samples for peritoneal cytology were taken. The group of 170 (24.1%) patients with intermediate risk of recurrence (IA G3, IB G1, G2) received teleradiotherapy alone. Of 535 (75.9%) patients with high risk of recurrence (IB-G3, IC, II) 230 (43%) received vaginal brachytherapy alone, and 305 (57%) received a combination of teleradiotherapy and vaginal brachytherapy.

Five-year disease-free survival after surgery was used as an efficacy measure. Log-rank test according to Peto et al. was used for assessment of significance of the observed differences in the studied material [19]. $P \leq 0.05$ was taken as the statistical significance level. Cox's proportional hazard model analysis was used to assess the influence of selected factors on survival rate [20].

Results

Of the 705 patients in the present group, 578 (82%) had a 5-year disease-free survival period. Relations between treatment outcome and demographic, clinical and microscopic features are presented in Table 1.

Table 1 shows that univariate analysis in our group detects the influence of age, cellular type of cancer, its differentiation degree and stage according to FIGO and depth of myometrial invasion on treatment outcome. A statistically significant higher 5-year disease-free survival rate was observed in patients younger than 60 years, with moderately and well differentiated cancers (G1 vs. G2 vs. G3), endometrioid adenocarcinoma (vs. other cancer types) in stage I (I vs. II), with less than 50% myometrial invasion. Parity and haemoglobin level did not display a significant influence on treatment outcome in univariate analysis.

Results of multivariate analysis according to Cox are presented in Table 2.

In the studied group of patients with endometrial cancer, treated with surgery followed by postoperative irradiation, degree of cancer differentiation was the only independent prognostic factor for 5-year disease-free survival in multivariate analysis.

Discussion

Multivariate analysis of prognostic factors in the group of 705 patients with non-advanced endometrial cancer, undergoing surgery followed by radiotherapy, was performed. Degree of cancer differentiation turned out to be the only independent prognostic factor. 90.9% of patients with well (G1), 80.2% with moderately (G2), and 64.1% with poorly (G3) differentiated cancer survived 5 years with no evidence of the disease.

These results are in accordance with the data from the literature, where the degree of cancer differentiation is unequivocally described as one of the primary factors influencing prognosis in patients with endometrial cancer [1,5–8,11,13,17,21–25].

Spaczyński et al. reported an 80% success rate in patients with well (G1), 74% moderately (G2) and 50% with poorly (G3) differentiated endometrial cancer [1]. Di Saia and Creasman reported:

Table 1. Treatment outcome in relation to demographic, clinical and microscopic features.

Demographic, clinical and microscopic features	Number of treated patients	5-year disease-free survival	
		Number of patients	%
Age*:			
below 60 years	366	315	86.1
60 and more years	339	263	77.6
Parity:			
nulliparous	126	103	81.7
uniparous	112	92	82.1
biparous	205	168	82.0
3 or more births	262	215	82.1
Duration of symptoms' presence:			
below 6 months	330	270	81.8
6 months and more	375	308	82.1
Cellular cancer type*:			
endometrioid adenocarcinoma	676	561	83.0
other	29	17	58.6
Haemoglobin level (g/dl):			
below 13	416	342	82.2
13 and more	289	236	81.7
Cancer staging according to FIGO (1988)*:			
IA	21	16	76.2
IB	180	169	93.9
IC	328	279	85.1
IIA	85	64	75.3
IIB	91	50	54.9
Cancer differentiation degree (G)*:			
G1	352	320	90.9
G2	197	158	80.2
G3	156	100	64.1
Depth of cancer myometrial invasion*:			
no invasion	21	16	76.2
less than 50%	297	261	87.9
more than 50%	387	301	77.8
Sum	705	578	82.0

* Difference statistically significant, log rank test: $p \leq 0.05$.

Table 2. Multivariate analysis results.

Feature	Relative risk	Significance p
Cancer differentiation degree:		
high (G1)	1.00	
medium (G2)	1.65	0.0029
low (G3)	2.48	0.0004

94%, 88% and 79% success rates, and Zaino et al. in a group of 597 patients: 91%, 82% and 66%, respectively [5,6]. Hachirsuga et al. described 10-year survival in 95% with well and 84% and 64% with moderately and poorly differentiated endometrial cancer, respectively [22]. Petterson in "Annual report on the results of treatment in gynecological cancer" from 1994 reported the following rates of 5-year survival in relation to differentiation degree of the endometrial cancer: in I – 89%, 82% and 69% (G1 vs. G2 vs. G3); in II – 75%, 65% and 52% [23]. Other authors reported success rates in stage I endometrial cancer ranging from 91% to 98% in well differentiated cancers, from 82% to 90% in moderately differentiated cancers and from 64% to 80% in poorly differentiated cancers [5,6,22].

Overall it is stressed in the literature that the lower differentiation degree, the higher probability of deep myometrial invasion and of extrauterine involvement [5,13,21,24,25]. Cheon et al. observed deep myometrial invasion in 12% of 210 patients with well differentiated cancer (G1), in 20% of 74 patients with moderately and in 46% of 70 patients with poorly differentiated cancer [26]. In GOG studies, Creasman et al. observed 23% of cases of myometrial invasion exceeding 2/3 of myometrial thickness in the group with well differentiated cancer and 58% in the group with poorly differentiated cancer [21]. Di Saia and Creasman reported 10%, 20% and 42% cases of deep myometrial invasion in patients with well, moderately and poorly differentiated endometrial cancer, respectively [5].

Degree of cancer differentiation influences significantly the probability of local lymph node involvement. Morrow reported that in his group of 70 patients with poorly differentiated cancer pelvic lymph node involvement was observed in 21.4% of cases, and of 440 patients with moderately and well differentiated cancer only in 4.1% [27]. Bonnier et al. observed pelvic lymph node metastases in 2–3% of patients with well differentiated, 10–15% with moderately and 18–25% with poorly differentiated stage I and II endometrial cancer [28].

It should be stressed that many authors consider moderate and especially poor differentiation degree as the primary indication for adjuvant, postoperative radiotherapy in patients with non-advanced endometrial cancer [6,9,29,30].

Univariate analysis showed that in the present group women younger than 60 years had a better prognosis compared to older patients. Data from the literature quite unequivocally point to worse prognosis in older women, although there are differences in assessment of prognostic age cut-off with a range between 60 and 70 years [1,6,7,9,11,17,23–25,31].

In our group the highest 5-year disease-free survival rate was observed in patients with endometrioid adenocarcinoma compared to other cellular cancer types [83.0% vs. 58.6%]. The literature reports emphasize the particularly bad prognosis in patients with clear cell cancer, and serous cancer [1,5,6,9,25,32]. Ziano et al. in a group of 597 subjects reported 5-year disease-free survival in: 82% of patients with endometrioid adenocarcinoma, 68% with clear cell cancer and 55% with serous cancer [6].

Undoubtedly, differentiation degree of the cancer is the primary prognostic factor in patients with endometrial cancer. In the present group the rate of 5-year disease-free survival decreased with the cancer stage [IB vs. IC vs. IIA vs. IIB], reaching: 93.9%, 85.1%, 75.3% and 54.9%, respectively. Altogether, of patients with stage I cancer 87.7% survived a 5-year disease-free period, and with stage II cancer, 64.8%; the difference was statistically significant.

Di Saia and Creasman report 86% 5-year survival for endometrial cancer in stage I and 66% in stage II [5]. Cicaric et al. described 93.5% 5-year survival in patients with stage IB cancer, 80.4% in stage IC and 82.8% in stage II [33]. Weiss et al. report 92% 5-year disease-free survival in patients with stage IA and IB cancers, 84% with stage IC and 79% with stage II [34].

In the present group depth of myometrial invasion was a prognostic factor, but only in the univariate analysis; the 5-year disease-free survival rate was significantly lower in patients with myometrial invasion of more than 50% of the myometrium thickness, compared to patients with lower degree of myometrial involvement [77.8% vs. 87.1%]. Based on data from the literature the depth of myometrial invasion is an established prognostic factor; deep invasion is connected with higher staging degree, with cellular types of cancer with poorer prognosis, and also with higher rate of pelvic lymph nodes metastases [1,6,9,13,17,21–26,28,35].

The studies on improvement of treatment efficacy in non-advanced endometrial cancer concentrate on several issues: improvement of

systemic treatment, as the most frequent reason for therapeutic failure is the spreading of the disease [new medications research]; improvement of radiotherapy [conformal radiotherapy, unconventional fractionation radiotherapy, radiosensitivity tests]; and search of biological factors enabling identification of patient groups with high recurrence risk – biological prognostic factors [1,5,8,13,14,16,31,36–40].

Conclusions

In a group of patients with non-advanced endometrial cancer treated with postoperative radiotherapy, degree of cancer differentiation is the primary prognostic factor.

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